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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,756	10/02/2003	Mary Jo Ondrechen	NU-593XX	6620

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EXAMINER	
AGRAWAL, RITESH	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/678,756	**Applicant(s)** ONDRECHEN ET AL.	
	Examiner Ritesh Agrawal	**Art Unit** 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 04-08-2004 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 04/06/2004.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/415,742, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. While said provisional application discloses claims 1-4, 6, 11, and 13-16, said provisional application does not disclose claims 5, or 7-10. With respect to claim 12, while said provisional application discloses identification of perturbed titration curves through visual inspection, said provisional application does not disclose identification of perturbed titration curved via statistical analysis or automated classification. Prior art published after the claimed prior application but before the filing date of the instant application may have been cited in this Office action. Applicants are requested to provide evidence that the elected invention is indeed disclosed in the prior application if they wish to contest the citation of prior art.

Information Disclosure Statement

The information disclosure statement filed on April 6th, 2004 has been entered and considered. Initialed copies of the form PTO-1449 are enclosed herein.

Drawings

The amended drawing filed April 8th, 2004 is not in compliance with 37 CFR 1.121(d) because (1) each sheet is not properly labeled "replacement sheet" and (2) the changes to the drawings (including the placement of multiple figures on single sheets) is not explained in detail. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Such code can be found on page 16 of the specifications and elsewhere.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-10 recite the limitation "said physical proximity". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 6, 11, 12, 13-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Ondrechen et al. (2001), (PNAS, 98, 12473-78).

The claims are drawn to a method for determining interaction sites in a protein.

With respect to independent claim 1, Ondrechen et al. disclose, "Analysis of the theoretical microscopic titration curves for all the ionizable residues of these proteins shows that a small fraction (3-7%) of the curves possess a flat region" (Abstract, lines 7-10). This coincides with the limitations of claim 1 to, "[identify] ionizable amino acid residues having anomalous predicted theoretical microscopic titration curve behavior." The reference further discloses, "the THEMATICS method identifies the location of the known active site from the cluster of positive results in coordinate space" (page 12476, 2nd column, 4th paragraph, lines 8-10). This coincides with the additional limitation of claim 1, "clustering certain of said identified ionizable amino acid residues into putative interaction sites."

With respect to dependent claim 2, the method disclosed by Ondrechen et al. comprises, "a computational method that identifies the active site of a protein . . . from a three-dimensional structure" (page 12476, 2nd column, 5th paragraph, lines 1-3); "calculating the pH dependent electrical potential caused by ionizable residues" (page 12477, 1st column, 6th paragraph, lines 1-2) which signifies that in calculating the pH dependent titration curves, an electrical potential function is being calculated. Ondrechen et al. further disclose that, "for each residue type, we have a plot with a family of curves: one plot with a curve for each Lys residue, another plot with a curve for each Arg residue, etc. We compare the curves for residues of the same type; curves with unusual shape are noted by visual inspection," (page 12473, 2nd column, 4th paragraph, lines 10-14). Step f of claim 2 is disclosed as above from page 12476, 4th paragraph, lines 8-10.

The limitations of claim 3 can be inferred from the fact that all residues of all residue types are examined for perturbed titration curve behavior (as cited above) but that only certain residues from this set fall into clusters. Hence, if the citation is identifying all perturbed residues and a subset of these cluster the citation is also identifying perturbed titration curve residues that do not cluster. As an example from the reference, for the TIM protein, four residues His-95, Glu-165, Lys-112 and Tyr-164 have perturbed curves (page 12474, 1st column, 4th paragraph, lines 2-4) but only three of the four cluster spatially, "Three of the four residues with perturbed titration curves are in close spatial proximity," (page 12474, 2nd column, 2nd paragraph, lines 1-2).

The limitations of claim 4 are disclosed in the abstract, "We show that theoretical microscopic titration curves (THEMATICS) can be used to identify active-site residues in proteins of known structure."

The limitations of claim 6 are disclosed in the legend of table 1, "Positive results that form a cluster in coordinate space," (page 12476, table 1, legend).

The limitations of claim 11 are disclosed as, "the perturbed titration curves in which partial protonation persists over a wide pH range," (page 12477, 2nd column, 1st paragraph, lines 27-28).

A species of claim 12 is disclosed as above on page 12473, 2nd column, 4th paragraph, lines 10-14.

The limitation of claim 13 is inferred from the reference to a catalytic site, "but is far enough away from the catalytic site, " (page 12476, 1st column, 1st paragraph, lines 2-3) in the discussion of identified active site residues.

The limitation of claims 14-15 is disclosed as, "K258 of 1AMQ is the residue that binds the cofactor," (page 12476, table 1, legend) wherein recognition must occur for binding to the cofactor.

In the absence of an explicit definition of the term ligand one where the term refers to anything that binds to a protein will be used. As such, the disclosure as stated above for claim 15 applies as a disclosure for claim 16 as well.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Oda et al. (1994), (Biochemistry, 33, 5275-5284).

The limitations of claim 1 are disclosed as, "[we] determine the pKa values of the carboxyl groups in the enzyme, " (page 5276, 1st column, 1st paragraph, lines 2-3). Which demonstrates a method for identifying ionizable amino acids. Furthermore, they disclose, "The pKa values were determined by a nonlinear least-squares fit of the titration curves to the theoretical titration curves," (page 5276, 2nd column, 5th paragraph, lines 1-3). Which demonstrates that they determined titration curves for each of the residues and that pKa values are directly dependent upon those curves. From this they identified two residues with perturbed pKa values (and, given the relationship between pKa and titration curves described above, residues which have perturbed titration curves), "the catalytic residues of Asp10 and 70 have unusual pKa values," (page 5283, 6th paragraph, lines 5-6). They then identified a group (cluster) of these as residues in the interaction site, "the protonation states of these carboxylates should govern the catalysis of the enzyme," (page 5286, 6th paragraph, lines 9-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ondrechen et al. (2001), (PNAS, 98, 12473-78) as applied to claim 2 above, and further in view of Sali (1998), (Nature Structural Biology, 5, 1029-1032).

The claim is drawn to a method for identifying protein active site residues from a protein structure where the protein structure is predicted from the amino acid sequence.

Ondrechen et al. disclose a method for identifying protein active site residues from a protein structure but do not disclose the prediction of said structure from a protein's amino acid sequence.

Sali teaches that," useful model [structures] can be obtained by fold assignment and comparative modeling for those protein sequences that are related to at least one known protein structure," (page 1029, 1st column, 1st paragraph, lines 10-14).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the predictive method of Ondrechen et al. such that they allowed for the determination of a protein's structure from its amino acid sequence. One having ordinary skill in the art would have been motivated to do this because, as suggested by Sali, " it is not feasible to determine the structure of every protein by experiment," and obtaining structures from amino acid sequence would allow one to analyze, "three-dimensional models for hundreds of thousands of . . . proteins, " from 10,000 protein structures, (page 1029, 1st column, 1st paragraph, lines 15-18).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ritesh Agrawal whose telephone number is (571) 272-2906. The examiner can normally be reached on 8:30 AM - 5:00 PM M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ritesh Agrawal RA

23 June 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER